RESPONSE

I. Status of the Claims

Claims 1-9 are pending.

II. Rejection of Claims 1-9 Under 35 U.S.C. § 101

The Action first maintains the rejection of claims 1-9 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well-established utility. Applicants in no way agree with the Examiner's position, however rather than reiterate the multitude of utilities and arguments presented in any of the Applicant's prior responses (Response to Paper nos. 9, 12, 14, 18 and 21) which are herein incorporated by reference Applicants will summarize their position and address directly the Examiner's comments in the latest Office Action (paper No 08132004).

First it may be useful to recall the standards of patentable utility as defined by the USPTO and the U.S. courts. Applicants respectfully submit that the legal test for utility involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections

under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin*, *supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Even under the newly installed utility guidelines, Applicants note that MPEP 2107 (II)(B)(1) states:

> (1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

In the specification Applicants asserted that the sequences of the present invention encode novel human membrane proteins (for example, in the title of the application) that share sequence and structural similarity with mammalian CD20 protein (specification at or about, page 1 line, 10-12; page 2, line 3; and page 15 line 18). As described in the specification (at page 1) such membrane protein receptor proteins play a role in the activation and release of agents that

mediate a variety of allergic and inflammatory reactions. Additionally the specification (on or about page 12, lines 7-9 describes the association of a person with a mutation in the sequences of the present invention manifesting the phenotype of, among others, connective tissue disorders. Thus, clearly Applicants have asserted that the protein encoded by the sequences of the present invention play a biological role in both immune function (allergic and inflammatory reactions) and connective tissue disorders.

Furthermore, Applicants have submitted evidence that the amino acid sequence of SEQ ID NO:2 of the present invention is identical to a sequence, Accession No. Q9H3V2 (information and alignment previously provided), which has been annotated by third party scientists *wholly unaffiliated with Applicants* as encoding "Membrane-spanning 4-domains subfamily A member 5 (testis-expressed transmembrane 4 protein) (CD20 antigen -like 2)". Clearly those of skill in the art would find Applicants' identification of the structural identity of the protein encoded by the sequences of the present invention as credible, since the same assertions have been made by several other third party scientists *wholly unaffiliated with Applicants (see for example previously provided exhibits of publications by* Ishibashi *, et al.*, 2001 (Gene *264*:87-93, 2001), Hulett *et al.*, 2001 (Biochem Biophys Res Commun 280:374-9, 2001), Liang and Tedder, 2001 (Genomics 72:119-27, 2001)and Liang, *et al.*, 2001 (Immunogenetics *53*:357-68, 2001).

Whilethese publications constitute evidence that clearly demonstrates that the protein of the present invention has a recognized utility that is accepted by those skilled in the art (see Example 10 of the Revised Interim Utility Guidelines Training Materials, pages 53-55), however, none of these publications emphasize the role of this protein in immune and inflammatory function or connective tissue disease that were asserted by Applicants in the instant specification.

Furthermore, Applicants belief in the utility of the sequences of the present invention was so great that they spent tens of thousands of dollars to create a transgenic "knockout" mice (as was described in the specification as filed, at least on or about page 2, lines 17-20) that were subject to a comprehensive medical work-up using an integrated suite of medical diagnostic procedures designed to assess the function of the major organ systems in a mammalian subject.

From this analysis additional clear and convincing evidence regarding the role of the protein encoded by the sequences of the claimed invention was provided by the evidence that disruption of the mouse ortholog of the claimed human sequences and thus elimination of the protein they encode, resulted in alterations in the immune and inflammatory response, specifically an increase in the level of natural killer (NK) cells that were detected in the blood

of animals in which this gene activity had been disrupted. This evidence was submitted in the form of a Declaration under 37 C.F.R. § 1.132 by Tamas Oravecz, Ph.D., the Director of Immunology at Lexicon Genetics Incorporated, that described these findings and their significance to those of skill in the art.

This Declaration clearly indicates that the protein encoded by the murine ortholog of the human sequences of the present invention plays a role in NK cell regulation. And clearly indicated that those of skill in the art recognize and would accept this as *in vivo* evidence that the protein encoded by the claimed human sequences also has a role in regulating the human immune and inflammatory response by modulating NK cell levels and further that NK cells are known to play a role in human connective tissue disorders such as Systemic Sclerosis. Therefore, Applicants' assertion in the specification as filed, that the molecules of the present invention play a role in immune and inflammatory responses and human connective tissue disorders like Systemic Sclerosis would be accepted and deemed as credible by those of skill in the art. Therefore, as a biologically validated regulatory protein involved in the regulation of NK cell levels and given the recognized role of NK cells in human connective tissue disorders like Systemic Sclerosis, the molecules of the present invention have a highly credible, well-recognized real world substantial and specific utility. Those of skill in the art would clearly recognize the utility of the present invention in addressing connective tissue disorders as well as be enabled to make and use the present invention without undue experimentation. Thus, the present invention clearly has credible specific and substantial real world utility and meets all of the requirements of 35 U.S.C. § 101.

In spite of the many forms of evidence that Applicants have provided supporting their original assertions regarding the utility and biological role of the sequences of the present invention, the Examiner, in spite of providing no objective evidence to the contrary, has elected to disregard these facts and argue that they are not persuasive.

First, the Examiner argues (on page 3) that "sequence homology with human CD20 antigen or other sequences present in databases does not render the present sequence a specific biological function or physiological significance because the state of the art in protein science indicates that it is impossible to predict protein functions based solely upon sequence homology."

This assertion is incorrect, as those of skill in the art clearly recognize a structure-function relationship (as has been evidenced exhaustively in previous responses), in fact, even the USPTO accepts that there is a structure function relationship when a high degree of homology exists

between a full length sequence and a protein having a known function. Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when a full length sequence has a similarity score greater than 95% to a protein having a known function.

In addition to being scientifically inaccurate and contradictory to PTO policy, this assertion is also *irrelevant* to the present case, as Applicants have submitted experimental evidence that clearly supports their original assertions regarding the biological role and utility as were made in the specification as filed.

In addition, the Examiner attempts to argue, on the bottom of page 3 onto page 4, that Applicants' previously submitted publication from Nature Reviews Drug Discovery (which demonstrates how findings in knockout mice are very often predictive of those in humans and thus establishes the value and utility of knockout mice in identifying drug targets to the pharmaceutical industry) somehow contradicts Applicants' assertions regarding the utility of the sequences of the present invention. Applicants assume this position results from the Examiner erroneously equating CD20 and its respective knockout mouse and findings submitted in regard to the instant case with the CD20-like molecules encoded by the sequences of the present invention. Applicants note that they have never asserted that the sequences of the present invention encode CD20 but rather that they encode a protein that is CD20-like.

Secondly, while the Examiner alleges to agree that one of skilled in the art would readily believe that the CD20-like protein encoded by the sequences of the present invention plays a role in the regulation of NK cells, that this was not disclosed in the application as originally filed (page 4). The Examiner then goes on to say that in view of the submitted evidence those of skill in the art would readily believe that reduced NK cell levels are associated with connective tissue disorders, "However, Applicants' knockout mouse showed an increased level of NK cells" and since in the submitted example of a connective tissue disorder the patients had a smaller percentage of NK cells, therefore, "Applicants' knockout mouse does not show, by any means, a causative link between the protein of the present invention and a connective tissue disorder" (bottom of page 4 through top of page 5).

Scientifically, such an argument is completely without merit. Clearly if one accepts that a protein regulates the levels of a cell type, that protein, by its increased or decreased

level/activity can regulate levels down or up, and thus act as either antagonist or agonist. For example in the instant case, if the absence of the CD20-like molecule encoded by the sequences of the present invention in the knockout mouse results in increased NK cell levels, then one would reasonably anticipate that increased levels of this molecule would have the opposite effect and lower the levels of NK cells, as has been reported in the specific connective tissue disorder provided in the evidence presented. Therefore there exists no logical contradiction in the evidence that Applicants have presented.

The very statement that "Applicants' knockout mouse does not show, by any means, a causative link between the protein of the present invention and a connective tissue disorder" is totally irrelevant to the present discussion and clearly emphasizes the improper standard for utility that many Examiners have recently adopted. The issue under 35 U.S.C. § 101 is **not** one of a causative human disease link but simply a credible, specific and substantial asserted utility or a well-established utility.

Applicants, in the specification as filed, asserted that the novel human membrane proteins encoded by the sequences of the present invention play a role in the activation and release of agents that mediate a variety of allergic and inflammatory reactions and that a mutation in the sequences of the present invention can manifest itself as a connective tissue disorder.

Applicants have provided experimental evidence, obtained using a method described in the specification as filed, and presented in a Declaration, that the protein encoded by the presently claimed sequences has an effect on the levels of inflammatory cells. The same inflammatory cells that have been shown, by unaffiliated third party scientists, to play a role in a recognized human connective tissue disorder.

Thus, as asserted **in the specification as filed**, the novel human membrane proteins encoded by the sequences of the present invention play a role in inflammatory reactions and that a mutation in the sequences of the present invention can manifest itself as a connective tissue disorder.

Therefore, without question the sequences of the present invention have been shown to have credible, specific and substantial real world utility that is recognized by those of skill in that art and that meets all of the requirements of 35 U.S.C. § 101.

Those of skill in the art would clearly recognize the utility of the present invention as well as be enabled to make and use the present invention without undue experimentation. Thus, the present invention clearly has credible and well established utility. In light of the evidence

presented above and in previous responses, Applicants respectfully submit that the present invention is in full compliance with the provisions of 35 U.S.C. § 101, and respectfully request that the rejection be withdrawn.

III. Rejection of Claims 1-9 Under 35 U.S.C. § 112, First Paragraph

The Action also rejects claims 1-9 under 35 U.S.C. § 112, first paragraph, as allegedly the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility allegedly one skilled in the art clearly would not know how to use the claimed invention. Applicants respectfully submit that claims 1-9 have been shown, using multiple forms of evidence to have "a specific, substantial, and credible utility", as detailed in the section II above. Therefore, one skilled in the art would clearly know how to use the claimed invention and Applicants therefore request that the rejection of claims 1-9 under 35 U.S.C. § 112, first paragraph, be withdrawn.

VI. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Li have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

January 24, 2005
Date

Lance K. Ishimoto Reg. No. No. 41,866
Agent for Applicants

LEXICON GENETICS INCORPORATED

Customer # 24231

(281) 863-3333